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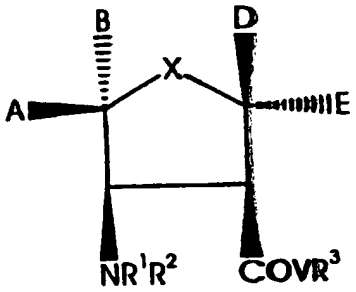
(57) Abstract

A method of combating fungi which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I), wherein X is O, S, SO, SO_2, NR^8 or CLM; A, B, D, E, L and M are, independently, hydrogen, halogen, alkyl, mono- or di-haloalkyl, benzyl (optionally substituted by halogen or haloalkyl) or hydroxy; A and B or D and E or L and M may together form a =S, =O or $=CR^6R^7$ group; B and L or D and L may together form a bond; V is O or NR^4; R^1 and R^2 are, independently, hydrogen or an amine protecting group; R^3, R^4 and R^8 are, independently, hydrogen, alkyl or benzyl; R^6 and R^7 are, independently, hydrogen, halogen, alkyl, phenyl, benzyl, alkoxy or acyloxy; or a salt thereof; provided that when X is CLM, R^1, R^2, R^3, A, M, D and E are all hydrogen, L and B are either both hydrogen or together form a bond, and V is O then the compound of formula (I) is in the form of a salt, but not a hydrochloride salt.



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FUNGICIDES

This invention relates to the use of 2-amino-cyclopentane- and cyclopentene-1-carboxylic acid derivatives to combat fungal infections of plants.

Various cyclopentane and cylopentene β-amino acid derivatives are disclosed in EP-A1-0571870. This document mentions the use of these compounds as pharmaceuticals.

According to the present invention there is provided a method of combating fungi which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I); wherein X is O, S, SO, SO_2, NR^8 or CLM; A, B, D, E, L and M are, independently, hydrogen, halogen, alkyl, mono- or di-haloalkyl, benzyl (optionally substituted by halogen or haloalkyl) or hydroxy; A and B or D and E or L and M may together form a =S, =O or $=CR^6R^7$ group; B and L or D and L may together form a bond; V is O or NR^4; R^1 and R^2 are, independently, hydrogen or an amine protecting group; R^3, R^4 and R^8 are, independently, hydrogen, alkyl or benzyl; R^6 and R^7 are, independently, hydrogen, halogen, alkyl, phenyl, benzyl, alkoxy or acyloxy; or a salt thereof; provided that when X is CLM, R^1, R^2, R^3, A, M, D and E are all hydrogen, L and B are either both hydrogen or together form a bond, and V is O then the compound of formula (I) is in the form of a salt, but not a hydrochloride salt.

The compounds of formula (I) are chiral and references to a compound of formula (I) cover each enantiomer individually and mixtures of enantiomers in all proportions.

Salts include acidic and basic salts, for example a salt of a haloacid (such as hydrochloric or hydrobromic acid), a salt of a phosphoric, nitric, sulphuric, carbonic, acetic, maleic, malonic, oxalic, gluconic, succinic, fumaric, tartaric, citric, salicylic, sorbic, lactic or sulphonic (such as p-toluenesulphonic, 1,5-naphthylidenesulphonic or camphorsulphonic) acid; or a salt of an alkali or alkaline earth method such as sodium, potassium, magnesium or calcium.

The term amine protecting group includes benzyl (optionally substituted by alkoxy or nitro), alkyl, acyl, haloalkyloxycarbonyl, alkenyloxycarbonyl, cycloalkyloxycarbonyl (optionally substituted by alkyl), alkyloxycarbonyl, phenyloxycarbonyl or phenylalkyloxycarbonyl (in

which the phenyl ring is optionally substituted by halogen, alkyl, haloalkyl, alkoxy or nitro) groups. Suitable amine protecting groups are, for example, benzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, allyloxycarbonyl, vinyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, phthaloyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-trichloro-tert-butoxycarbonyl, menthyloxycarbonyl, 4-nitrophenoxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, acetyl, propionyl, pivalonyl, 2-chloroacetyl, 2-bromoacetyl, 2,2,2-trifluoracetyl, 2,2,2-trichloracetyl, benzoyl, benzyl, 4-chlorobenzoyl, 4-bromobenzyl, 4-nitrobenzoyl, phthalimide, isovaleroyl, benzyloxymethylene, 4-nitrobenzyl, 2,4-dinitrobenzyl, 4-nitrophenyl or 2-nitrophenylsulphonyl.

Cycloalkyl preferably contains from 3 to 7, more preferably 5 or 6, carbon atoms and is, for example, cyclohexane.

All alkyl groups and the alkyl moiety of haloalkyl and alkoxy preferably contain from 1 to 8, more preferably from 1 to 6, especially from 1 to 4, carbon atoms. They can be straight or branched chain and are, for example, methyl, ethyl, n-propyl, n-butyl or tert-butyl.

Acyl groups and the acyl moiety of acyloxy are preferably formyl, alkylcarbonyl (in which the alkyl group is optionally substituted by halogen) or phenylcarbonyl (in which the phenyl ring is optionally substituted by halogen, nitro, alkyl or alkoxy) groups, and are, for example, formyl, acetyl, 2,2,2-trifluoracetyl or benzoyl.

Alkenyl preferably contains from 2 to 6, especially from 2 to 4, carbon atoms in the form of straight or branched chains. Examples are vinyl and allyl.

Halogen includes iodine and bromine but is especially chlorine or fluorine.

Unless specified otherwise there is no restriction on the number of halogen atoms in a haloalkyl group. The halogen atoms in haloalkyl groups are preferably fluorine or chlorine atoms. Haloalkyl is, for example, FCH_2, F_2CH, CF_3, CCl_3, CF_2CF_3, CH_2CF_3, CH_2CF_3, CH_2CHF_2 or $CHFCH_2F$.

In one aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1); wherein A, B, D, E, L and M are, independently, hydrogen, halogen, alkyl, mono- or di-haloalkyl or hydroxy; or A and B or D and E or L and M many together form a $=CR^6R^7$ group; or B and L or D and L may together form a bond; R^6 and R^7 are, independently, hydrogen, halogen, alkyl, phenyl, benzyl, alkoxy or acyloxy; R^1 is hydrogen and R^2 is hydrogen or an amine protecting group; and R^3 is hydrogen, alkyl or benzyl; or a salt thereof.

In a further aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1b); wherein L and M are independently hydrogen, halogen, alkyl, mono- or di-haloalkyl or hydroxy; and R^1, R^2 and R^3 are as defined above; or a salt thereof.

In a still further aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1c); wherein D and E are independently hydrogen, halogen, alkyl, mono- or di-haloalkyl or hydroxy; and R^1, R^2 and R^3 are as defined above; or a salt thereof.

In a further aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1c); where in D is hydrogen, E is alkyl (preferably methyl), and R^1, R^2 and R^3 are as defined above (but are preferably all methyl); or a salt (especially a hydrochloride salt) thereof.

In yet another aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1d); wherein A is hydrogen, halogen, alkyl, mono- or di-haloalkyl or hydroxy; and R^1, R^2 and R^3 are as defined above; or a salt thereof.

In a further aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1e); wherein M is hydrogen, halogen, alkyl, mono- or di-haloalkyl or hydroxy; and R^1, R^2 and R^3 are as defined above, or a salt thereof.

In a still further aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1f); wherein M is hydrogen, halogen, alkyl, mono- or di-haloalkyl or hydroxy; and R^1, R^2 and R^3 are as defined above; or a salt thereof.

In another aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1g); wherein E is hydrogen, halogen, alkyl, mono- or di-haloalkyl or hydroxy; and R^1, R^2 and R^3 are as defined above; or a salt thereof.

In yet another aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1h); wherein R^6 and R^7 are, independently, hydrogen, halogen, alkyl, phenyl, benzyl, alkoxy or acyloxy; and R^1, R^2 and R^3 are defined as above, or a salt thereof.

In a still further aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1i); wherein R^6 and R^7 are, independently, hydrogen, halogen, alkyl, phenyl, benzyl, alkoxy or acyloxy; and R^1, R^2 and R^3 are as defined above, or a salt thereof.

In a further aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1i); wherein R^6 and R^7 are, independently, hydrogen, halogen or alkyl (especially methyl); and R^1, R^2 and R^3 are as defined above (but are preferably all hydrogen); or a salt (especially a hydrochloride salt) thereof.

In another aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1j); wherein R^6 and R^7 are, independently, hydrogen, halogen, alkyl, phenyl, benzyl, alkoxy or acyloxy; and R^1, R^2 and R^3 are as defined above, or a salt thereof.

In yet another aspect the present invention provides a method as described above wherein R^1, R^2 and R^3 are all hydrogen.

In a further aspect the present invention provides an agricultural composition wherein compound 40 of Table I, or a salt or ester thereof, is in admixture with compound 1 of Table I, or a salt or ester thereof.

In yet another aspect the present invention provides a method which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant compound 40 of Table I, or a salt or ester thereof, in admixture with compound 1 of Table I, or a salt or ester thereof.

In a further aspect the present invention provides a compound of formula (I.2) wherein:

i) L and R^3 are H, M is F and R^3 is H or tert-butoxycarbonyl; or

ii) L and M are F, R^3 is tert-butoxycarbonyl and R^1 is H or CH_3; or

iii) L and M together with the carbon to which they are attached form C=O, R^1 is methyl and R^3 is H, tert-butoxycarbonyl, $C(O)N_3$ or $C(O)NHC(O)OC(CH_3)_3$; or

iv) L is OH, M is H, R^1 is CH_3 and R^3 is tert-butoxycarbonyl;

or a salt thereof.

In a still further aspect the present invention provides a compound of formula (I.3); wherein R^1 is tert-butoxycarbonyl, R^3 is CH_3 and X is SO_2, SO, NH or $NCH_2C_6H_5$; or R^1 and R^3 are both H and X is NH; or R^1 is tert-butoxycarbonyl, R^3 is $CH_2C_6H_5$ and X is oxygen; or a salt thereof.

In another aspect the present invention provides a compound of formula (I.1), wherein R^1, R^2, R^3, A and M are all hydrogen and:

i) B is fluorine and L, D and E are all hydrogen;

ii) L is fluorine and B, D and E are all hydrogen;

iii) D is fluorine, ethyl, tert-butyl or benzyl and B, L and E are all hydrogen;

iv) E is fluorine and B, L and E are all hydrogen; or

v) D and E together form $=CH_2$ and B and L are both hydrogen;

or a salt thereof.

Examples of compounds of formulae (I.1) and (I.3) are presented in Tables I and II respectively.

TABLE I

Compound No.	A	B	L	M	D	E	R^1	R^2	R^3
1*	H	H	H	H	CH_3	H	H	H	H
2*	H	H	H	F	H	H	H	H	H
3*	CH_3	H	H	H	H	H	H	H	H
4	H	H	H	F	H	H	H	BnOC	CH_3
5*	H	H	F	F	H	H	H	H	H
6	H	H	=O		H	H	H	NBOC	CH_3
7	H	H	=O		H	H	H	BOC	CH_3
8	H	H	=O		H	H	H	C(O)N_3	CH_3
9	H	H	F	F	H	H	H	BOC	CH_3
10	H	H	F	F	H	H	H	BOC	H
11	H	H	=O		H	H	H	BnOC	CH_3
12	H	H	OH	H	H	H	H	BnOC	CH_3
13*	H	H	=O		H	H	H	H	CH_3
14*	H	H	=O		H	H	H	H	H
15	H	H	H	H	H	H	H	BnOC	CH_3
16	H	H	H	H	H	H	H	C(O)CH(NH_2)$CH_2C_6H_5$	H
17	H	H	H	H	H	H	H	C(O)CH(NHBOC)$CH_2C_6H_5$	CH_3
18	H	H	H	H	H	H	H	C(O)CH(NHBOC)$CH_2C_6H_5$	H
19	H	H	H	H	H	H	H	C(O)CH(NH_2)$CH_2C_6H_5$	CH_3
20	H	H	H	H	H	H	H	C(O)(4-CH_3O-C_6H_4)	CH_3
21	H	H	H	H	H	H	H	BOC	C_6H_5
22	H	H	H	H	H	H	H	BOC	$CH_2C_6H_5$
23	H	H	H	H	H	H	H	BOC	H
24	H	H	H	H	H	H	H	BOC	CH_3
25	H	H	H	H	H	H	H	H	$CH_2C_6H_5$
26	H	H	H	H	H	H	H	CH_3	H
27	H	CH_3	H	H	H	H	H	H	H
28	H	CH_2OH	H	H	H	H	H	H	H
29	H	F	H	H	H	H	H	H	H
30*	=CH_2	H	H	H	H	H	H	H	

TABLE I (Continued)

Compound No.	A	B	L	M	D	E	R^1	R^2	R^3
31	H	H	F	H	H	H	H	H	H
32*	H	H	$=CH_2$		H	H	H	H	H
33*	H	H	CH_3	CH_3	H	H	H	H	H
34*	H	H	CH_3	H	H	H	H	H	H
35	H	H	H	H	$=CH_2$		H	H	H
36*	H	H	H	CH_3	H	H	H	H	H
37	H	H	H	H	F	H	H	H	H
38	H	H	H	H	C_2H_5	H	H	H	H
39	H	H	H	H	H	C_2H_5	H	H	H
40*	H	H	H	H	H	CH_3	H	H	H
41	H	H	H	H	$(CH_3)_3C$	H	H	H	H
42	H	H	H	H	$C_6H_5CH_2$	H	H	H	H
43	H	H	H	H	H	F	H	H	H

* Compounds are hydrochloride salts.

TABLE II

Compound No.	X	R^1	R^3	Salt (where present)
1	O	H	H	
2	S	H	H	
3	O	BnOC	$CH_2C_6H_5$	
4	SO_2	BOC	CH_3	
5	SO	BOC	CH_3	
6	SO	H	H	HCl
7	SO_2	H	H	HCl

TABLE II (Continued)

Compound No.	X	R^1	R^3	Salt (where present)
8	$NCH_2C_6H_5$	BOC	CH_3	
9	NH	BOC	CH_3	
10	$NCH_2C_6H_5$	H	H	HCl
11	O	H	H	
12	NH	H	H	HCl

In Tables I and II the abbreviations BOC, BnOC and NBOC appearing as values of, or as a part of a value of, R^1 or R^2 have the following meanings:

BOC is tert-butyloxycarbonyl.

BnOC is benzyloxycarbonyl.

NBOC is tert-butyloxycarbonylaminocarbonyl.

TABLE III

Table III shows melting point, selected mass spectral or selected proton NMR data for certain compounds described in Tables I and II. Chemical shifts are measured in ppm from tetramethylsilane. Spectra were recorded on an instrument operating at 270 MHz and unless otherwise stated deuterochloroform was used as solvent. The following abbreviations are used:

s = singlet
t = triplet
q = quartet
br = broad
d = doublet
m = multiplet
dd = double doublet
ppm = parts per million
dt = double triplet

Compound No. (Table No.)	Data
6(I)	111-116.5°C
8(I)	2.36-2.80(4H,m); 3.49(1H,m); 3.76(3H,s); 4.70(1H,dt); 6.15(1H,d)ppm.
15(I)	1.52-2.07(6H,m); 3.00(1H,m); 3.61(3H,s); 4.28(1H,m); 5.19(2H,s); 5.29(1H,br s); 7.33(5H,s)ppm.
16(I)	110-124°C
17(I)	120-122.5°C
18(I)	81.5-84°C
19(I)	61-64°C
20(I)	123-125°C
21(I)	116-117°C
22(I)	70.5-72.5°C
23(I)	1.48(9H,s); 1.30-2.20(6H,m); 2.95-3.16(1H,m); 3.96-4.35(1H,m); 5.23(br d); 6.82(br d); 11.75(1H, br s)ppm.
24(I)	1.43(9H,s); 1.49-1.74(2H,m); 1.74-2.08(4H,m); 3.01(1H,m); 3.68(3H,m); 4.23(1H,br m); 4.95(1H,br d)ppm.
25(I)	1.60(2H,m); 1.98(4H,m); 2.63(2H,br s); 2.89(1H,m); 3.65(1H,m); 5.15(2H,s); 7.36(5H,s)ppm.
26(I)	144-149°C.
33(I)	0.97(3H,s); 1.15(3H,s); 1.55(1H,m); 1.68(1H,m); 1.76(1H,m); 1.95(1H,m); 3.14(1H,m); 3.49(1H,m); 3.68(3H,s); 3.74(2H,d) 7.28(5H,m)ppm.
1(II)	203.5-205°C
2(II)	2.74(1H,dd); 2.96-3.28(4H,m); 3.76(3H,s); 3.98(1H,br m)ppm.
4(II)	123.2-125.2°C
5(II)	1.42(9H,s); 2.76(1H,dd); 3.00-3.70(4H,m); 3.76(3H,s); 5.18(1H,br m); 6.25(1H,br d)ppm.
6(II)	MH^+ 164
7(II)	[D_2O as solvent]3.47-3.92(5H,m); 4.42(1H,br dd)ppm.

Compound No. (Table No.)	Data
9(II)	1.43(9H,s); 2.94(1H,dd); 3.14-3.40(4H,m); 3.71(3H,s); 4.47(1H,br s); 5.22(1H,br s)ppm.
11(II)	200-202°C
12(II)	[D_2O as solvent] 3.31-3.84(5H,m); 4.15(dd); 4.21(dd)ppm.

The compounds of formula (I) can be made by adapting methods known in the literature, for example known from EP-A1-0571870, EP-A1-0538692 or EP-A1-0538688.

Certain compounds of formula (I) can be prepared as shown in Scheme 1. Throughout Scheme 1 A, B, D, E and X are as defined above, R^3 is as defined above but is not hydrogen and R* is alkyl, phenyl or phenylalkyl, the phenyl rings being optionally substituted with alkyl, halogen, haloalkyl, alkoxy or nitro. Thus, the present invention provides a process for the preparation of a compound of formula (A) which comprises reacting a compound of formula (B) with an alcohol of formula R*OH in the presence of a solvent (which is, preferably, an excess of the alcohol of formula R*OH) at a suitable temperature, for example in the range 20-150°C.

In another aspect the present invention provides a process for preparing a compound of formula (A) comprising reacting a compound of formula (C) with an azide (such as sodium azide or trimethylsilylazide) in a suitable solvent or solvent mixture (such as water and dichloromethane), and reacting the product formed with an alcohol of formula R*OH. It is preferred that when the solvent mixture is a mixture of immiscible solvents a suitable phase transfer reagent is used (such as tetra-n-butylammonium bromide.

In a further aspect the present invention provides a process for the preparation of a compound of formula (A) comprising the steps: (a) reacting a compound of formula (D) with an acid chloride (such as oxalyl chloride or thionyl chloride) optionally in the presence of a catalyst (such as N,N-dimethylformamide) and in the presence of a suitable solvent; (b)

reacting the product of (a) with an azide; and (c) reacting the product of (b) with an alcohol of formula R*OH.

In relation to compounds 1 and 40 of Table I salts are preferably acidic and basic salts, for example, a salt of an inorganic acid such as a hydrochloride salt, a salt of an organic acid such as a tosylate or a dodecylbenzene sulphonic acid salt, an alkali or alkaline earth metal salt such as a sodium, potassium or calcium salt, a mono- or dialkylamine salt such as an octylamine salt, a sulphate salt or an ammonium salt; while esters are preferably alkyl, alkenyl and alkynyl esters wherein the alkyl group contains, for example, from 1 to 8 carbon atoms in a straight or branched chain; and the alkenyl and alkynyl groups contain, for example, from 3 to 8 carbon atoms in a straight or branched chain. Examples are methyl, ethyl, n-propyl, iso-propyl, n-, iso-, sec- and tert-butyl, allyl and propargyl. Salts of esters, such as hydrochloride salt of an ester, are included in the present invention.

Compounds 1 and 40 of Table I can be prepared by reacting 3-methylcyclopent-1-ene with chlorosulphonyl isocyanate in a suitable solvent (such as dichloromethane) to produce a mixture of β-lactams. Optionally, the nitrogen of the β-lactams can be protected with a silyl group (such as a tert-butyldimethylsilyl group).

The β-lactam or protected β-lactam can be ring opened and deprotected by reaction with a strong mineral acid (such as concentrated hydrochloric acid).

The compounds of formula (I) show fungicidal activity across a range of plant diseases. They are, however, particularly active against the class of pathogens known as the phycomycetes (equivalent to the oomycetes). These include species of Phytophthora, Plasmopara, Peronospora and Pseudoperonospora. Examples of pathogens which the invention compounds are particularly useful for controlling are: Plasmopara viticola on vines; other downy mildews such as Bremia lactucae on lettuce; Peronospora spp. on soybeans, tobacco, onions and other hosts; Pseudoperonospora humuli on hops and Pseudoperonospora cubensis on cucurbits; Phytophthora infestans on potatoes and tomatoes and other Phytophthora spp. on vegetables, strawberries, avocado, pepper, ornamentals, tobacco, cocoa and other hosts; and Pythium spp. on rice, horticultural plants, vegetables and turf.

The compounds of formula (I) may move acropetally/locally in plant tissue. Moreover, the compounds may be volatile enough to be active in the vapour phase against fungi on the plant.

The compounds of formula (I) may be used directly for agricultural purposes but are more conveniently formulated into compositions using a carrier or diluent. It is preferred that all compositions, both solid and liquid formulations, comprise 0.0001 to 95%, more preferably 1 to 85%, for example 1 to 25% or 25 to 60%, of a compound of formula (I).

When applied the foliage of plants, the compounds of formula (I) are applied at rates of 0.1g to 10Kg, preferably 1g to 8Kg, more preferably 10g to 4Kg, of active ingredient per hectare.

When used as seed dressings, the compounds of formula (I) are used at rates of 0.0001g (for example 0.001g or 0.05g) to 10g, preferably 0.005g to 8g, more preferably 0.005g to 4g, of active ingredient per kilogram of seed.

The compounds of formula (I) can be applied in a number of ways. For example, they can be applied, formulated or unformulated, directly to the foliage of a plant, to seeds or to other medium in which plants are growing or are to be planted, or they can be sprayed on, dusted on or applied as a cream or paste formulation, or they can be applied as a vapour or as slow release granules.

Application can be to any part of the plant including the foliage, stems, branches or roots, or to soil surrounding the roots, or to the seed before it is planted, or to the soil generally, to paddy water or to hydroponic culture systems. The compounds of formula (I) may also be injected into plants or sprayed onto vegetation using electrodynamic spraying techniques or other low volume methods.

The term "plant" as used herein includes seedlings, bushes and trees. Furthermore, the fungicidal method of the invention includes preventative, protectant, prophylactic, systemic and eradicant treatments.

The compounds of formula (I) are preferably used for agricultural and horticultural purposes in the form of a composition. The type of composition used in any instance will depend upon the particular purpose envisaged.

The compositions may be in the form of dustable powders or granules comprising the active ingredient and a solid diluent or carrier, for

example, fillers such as kaolin, bentonite, kieselguhr, dolomite, calcium carbonate, talc, powdered magnesia, fuller's earth, gypsum, diatomaceous earth and china clay. Such granules can be preformed granules suitable for application to the soil without further treatment. These granules can be made either by impregnating pellets of filler with the active ingredient or by pelleting a mixture of the active ingredient and powdered filler. Compositions for dressing seed may include an agent (for example, a mineral oil) for assisting the adhesion of the composition to the seed; alternatively the active ingredient can be formulated for seed dressing purposes using an organic solvent (for example, N-methylpyrrolidone, propylene glycol or N,N-dimethylformamide). The compositions may also be in the form of wettable powders or water dispersible granules comprising wetting or dispersing agents to facilitate the dispersion in liquids. The powders and granules may also contain fillers and suspending agents.

The compositions may also be in the form of soluble powders or granules, or in the form of solutions in polar solvents.

Soluble powders may be prepared by mixing the active ingredient with a water-soluble salt such as sodium bicarbonate, sodium carbonate, magnesium sulphate or a polysaccharide, and a wetting or dispersing agent to improve water dispersibility/solubility. The mixture may then be ground to a fine powder. Similar compositions may also be granulated to form water-soluble granules. Solutions may be prepared by dissolving the active ingredient in polar solvents such as ketones, alcohols and glycol ethers. These solutions may contain surface active agents to improve water dilution and prevent crystallisation in a spray tank.

Emulsifiable concentrates or emulsions may be prepared by dissolving the active ingredient in an organic solvent optionally containing a wetting or emulsifying agent and then adding the mixture to water which may also contain a wetting or emulsifying agent. Suitable organic solvents are aromatic solvents such as alkylbenzenes and alkylnaphthalenes, ketones such as cyclohexanone and methylcyclohexanone, chlorinated hydrocarbons such as chlorobenzene and trichlorethane, and alcohols such as benzyl alcohol, furfuryl alcohol, butanol and glycol ethers.

Suspension concentrates of largely insoluble solids may be prepared by ball or bead milling with a dispersing agent with a suspending agent included to stop the solid settling.

Compositions to be used as sprays may be in the form of aerosols wherein the formulation is held in a container under pressure of a propellant, e.g. fluorotrichloromethane or dichlorodifluoromethane.

The compounds of formula (I) can be mixed in the dry state with a pyrotechnic mixture to form a composition suitable for generating in enclosed spaces a smoke containing the compounds.

Alternatively, the compounds may be used in micro-encapsulated form. They may also be formulated in biodegradable polymeric formulations to obtain a slow, controlled release of the active substance.

By including suitable additives, for example additives for improving the uptake, distribution, adhesive power and resistance to rain on treated surfaces, the different compositions can be better adapted for various utilities. Other additives may be included to improve the biological efficacy of the various formulations. Such additives can be surface active materials to improve the wetting and retention on surfaces treated with the formulation and also the uptake and mobility of the active material, or additionally can include oil based spray additives, for example, certain mineral oil and natural plant oil (such as soya bean and rape seed oil) additives, or blends of them with other adjuvants.

The compounds of formula (I) can be used as mixtures with fertilisers (e.g. nitrogen-, potassium- or phosphorus-containing fertilisers). Compositions comprising only granules of fertiliser incorporating, for example coated with, a compound of formula (I) are preferred. Such granules suitably contain up to 25% by weight of the compound.

Wettable powders, emulsifiable concentrates and suspension concentrates will normally contain surfactants, e.g. a wetting agent, dispersing agent, emulsifying agent or suspending agent. These agents can be cationic, anionic or non-ionic agents.

Suitable cationic agents are quaternary ammonium compounds, for example, cetyltrimethylammonium bromide. Suitable anionic agents are soaps, salts of aliphatic monoesters of sulphuric acid (for example, sodium lauryl sulphate), and salts of sulphonated aromatic compounds (for example, sodium dodecylbenzenesulphonate, sodium, calcium or ammonium lignosulphonate, butylnaphthalene sulphonate, and a mixture of sodium diisopropyl- and triisopropylnaphthalene sulphonates).

Suitable non-ionic agents are the condensation products of ethylene oxide with fatty alcohols such as oleyl or cetyl alcohol, or with alkyl phenols such as octyl- or nonylphenol and octylcresol. Other non-ionic agents are the partial esters derived from long chain fatty acids and hexitol anhydrides, the condensation products of the said partial esters with ethylene oxide, and the lecithins. Suitable suspending agents are hydrophilic colloids (for example, polyvinylpyrrolidone and sodium carboxymethylcellulose), and swelling clays such as bentonite or attapulgite.

Compositions for use as aqueous dispersions or emulsions are generally supplied in the form of a concentrate containing a high proportion of the active ingredient, the concentrate being diluted with water before use. These concentrates should preferably be able to withstand storage for prolonged periods and after such storage be capable of dilution with water in order to form aqueous preparations which remain homogeneous for a sufficient time to enable them to be applied by conventional spray equipment. The concentrates may conveniently contain up to 95%, suitably 1-85%, for example 1-25% or 25-60%, by weight of the active ingredient. After dilution to form aqueous preparations, such preparations may contain varying amounts of the active ingredient depending upon the intended purpose, but an aqueous preparation containing 0.0001 to 10%, for example 0.005 to 10%, by weight of active ingredient may be used.

The compositions may contain other compounds having biological activity, e.g. compounds having similar or complementary fungicidal activity or which possess plant growth regulating, herbicidal or insecticidal activity.

An additional fungicidal compound may be present in the composition. By including another fungicide, the resulting composition can have a broader spectrum of activity or a greater level of intrinsic activity than the compound of formula (I) alone. Further the other fungicide can have a synergistic effect on the fungicidal activity of the compound of formula (I). Examples of fungicidal compounds which may be included in the composition are (RS)-1-aminopropylphosphonic acid, (RS)-4-(4-chlorophenyl)-2-phenyl-2-(1H-1,2,4-triazol-1-ylmethyl)butyronitrile, (Z)-N-but-2-enyloxymethyl-2-chloro-2',6'-diethylacetanilide, 1-(2-cyano-2-methoxyiminoacetyl)-3-ethyl urea, 4-(2,2-difluoro-1,3-benzodioxol-4-yl)-

pyrrole-3-carbonitrile, 4-bromo-2-cyano-N,N-dimethyl-6-trifluoromethyl-benzimidazole-1-sulphonamide, 5-ethyl-5,8-dihydro-8-oxo(1,3)-dioxol-(4,5-g)quinoline-7-carboxylic acid, α-[N-(3-chloro-2,6-xylyl)-2-methoxy-acetamido]-g-butyrolactone, N-(2-methoxy-5-pyridyl)-cyclopropane carboxamide, alanycarb, aldimorph, ampropylfos, anilazine, azaconazole, BAS 490F, benalaxyl, benomyl, biloxazol, binapacryl, bitertanol, blasticidin S, bromuconazole, bupirimate, butenachlor, buthiobate, captafol, captan, carbendazim, carbendazim chlorhydrate, carboxin, chinomethionate, chlorbenzthiazone, chloroneb, chlorothalonil, chlorozolinate, clozylacon, copper containing compounds such as copper oxychloride, copper oxyquinolate, copper sulphate, copper tallate, and Bordeaux mixture, cycloheximide, cymoxanil, cyproconazole, cyprofuram, debacarb, di-2-pyridyl disulphide 1,1'-dioxide, dichlofluanid, dichlone, diclobutrazol, diclomezine, dicloran, didecyl dimethyl ammonium chloride, diethofencarb, difenoconazole, O,O-di-iso-propyl-S-benzyl thiophosphate, dimefluazole, dimetconazole, dimethomorph, dimethirimol, diniconazole, dinocap, dipyrithione, ditalimfos, dithianon, dodemorph, dodine, doguadine, edifenphos, epiconazole, etaconazole, ethirimol, ethoxyquin, ethyl (Z)-N-benzyl-N-([methyl(methyl-thioethylideneamino-oxycarbonyl)amino]thio)--β-alaninate, etridiazole, fenaminosulph, fenapanil, fenarimol, fenbuconazole, fenfuram, fenpiclonil, fenpropidin, fenpropimorph, fentin acetate, fentin hydroxide, ferbam, ferimzone, fluazinam, fludioxonil, fluoroimide, fluquinconazole, flusilazole, flutolanil, flutriafol, folpet, fuberidazole, furalaxyl, furconazole-cis, guazatine, hexaconazole, hydroxyisoxazole, hymexazole, ICIA5504, imazalil, imibenconazole, ipconazole, iprobenfos, iprodione, isopropanyl butyl carbamate, isoprothiolane, kasugamycin, mancozeb, maneb, mepanipyrim, mepronil, metalaxyl, metconazole, methfuroxam, metiram, metiram-zinc, metsulfovax, myclobutanil, NTN0301, neoasozin, nickel dimethyldithiocarbamate, nitrothal-isopropyl, nuarimol, ofurace, organomercury compounds, oxadixyl, oxolinic acid, oxycarboxin, pefurazoate, penconazole, pencycuron, phenazin oxide, phosetyl-Al, phosphorus acids, phthalide, polyoxin D, polyram, probenazole, prochloraz, procymidone, propamocarb, propamocarb hydrochloride, propiconazole, propineb, propionic acid, prothiocarb, pyracarbolid, pyrazophos, pyrifenox, pyrimethanil, pyroquilon, pyroxyfur, pyrrolnitrin, quaternary ammonium compounds, quinconazole, quinomethionate,

quintozene, rabenazole, sodium pentachlorophenate, streptomycin, sulphur, tebuconazole, techlofthalam, tecnazene, tetraconazole, thiabendazole, thicyofen, thifluzamide, 2-(thiocyanomethylthio)benzothiazole, thiophanate-methyl, thiram, timibenconazole, tolclofos-methyl, tolylfluanid, triacetate salt of 1,1'-iminodi(octamethylene)diguanidine, triadimefon, triadimenol, triazbutyl, triazoxide, tricyclazole, tridemorph, triforine, triflumizole, triticonazole, validamycin A, vapam, vinclozolin, XRD-563, zineb and ziram. The compounds of formula (I) can be mixed with soil, peat or other rooting media for the protection of plants against seed-borne, soil-borne or foliar fungal diseases.

The following Examples illustrate methods by which compounds of formula (I) can be prepared. Where it is used in the following Examples, DISPERSOL is a Trade Name or Trade Mark.

Where shown, NMR data are selective; no attempt has been made to list every absorption in all cases. The following abbreviations are used throughout:

d = doublet	dd = double doublet
NMR = nuclear magnetic resonance	t = triplet
DMF = N,N-dimethylformamide	m.pt. = melting point

EXAMPLE 1

This Example shows the preparation of a 9:1 mixture of the racemic compounds 40 of Table I: 1 of Table I.

Step 1

In dry apparatus under nitrogen and at 0°C, chlorosulphonyl isocyanate (8.61ml, 0.099M) was dissolved in dry dichloromethane (10ml) with stirring. A solution of racemic 3-methylcyclopent-1-ene (12.78ml, 0.119M) in dry dichloromethane was gradually added dropwise. The resulting pale yellow solution was stirred at 20°C for 3 days.

The solution was then added dropwise and with vigorous stirring to a mixture of potassium iodide (0.3g), sodium sulphite (0.35g) and sodium bicarbonate (24g) in water (40ml) at 0-5°C. The pH of the reaction mixture was monitored and kept between pH 5-7 by the addiiton of 10% aqueous sodium hydroxide solution when necessary. When hydrolysis was complete the mixture was stirred at 5°C for 15 minutes and the organic layer separated. The aqueous layer was extracted with dichloromethane twice, the organic

extracts were combined, washed with brine, dried (over anhydrous magnesium sulphate) and concentrated under reduced pressure to leave an oil. Trituration of the oil with pentane and a little diethyl ether gave a mixture of compounds of formula (V) (all racemates) as a solid, melting point 90-92°C.

Step 2

To a mixture of compounds of formula (V) (as produced in Step 1, 0.50g, 0.004M) and triethylamine (0.61ml, 0.004M) in dry dichloromethane (10ml), under nitrogen at 20°C, was carefully added, with stirring, tert-butyldimethylsilyl triflate (1.01ml, 0.0044M). The reaction mixture was stirred at 20°C for 2 hours and then allowed to stand for 2-3 days. The reaction mixture was concentrated under reduced pressure and the resulting oil was partitioned between water and diethyl ether. The organic layer was separated and the aqueous was extracted twice with further amounts of diethyl ether. The organic layers were combined, washed with brine, dried (over anhydrous magnesium sulphate) and concentrated under reduced pressure to leave a pale yellow oil. Preparative liquid chromatography using a mobile phase of 9:1 hexane:ethyl acetate provided a 9:1 mixture (by gas chromatography) of compounds (VI) (as a racemate).

Step 3

A 9:1 mixture of compounds (VI) (as prepared in Step 2, 0.894g) was stirred with concentrated hydrochloric acid (6ml) and water (1ml) at 0°C for 1 hour, and then at 20°C for 3 hours. The reaction mixture was concentrated under reduced pressure and the resulting oil was taken up in a little acetone. Ice cooling and scratching gave the title mixture as a solid which was filtered, washed with acetone and air dried (0.584g; melting point: 152°C softens, 156-9°C decomposes). ^{1}H NMR of (IIa) one component: 0.95(3H,d), 1.08-2.35(5H, complex), 3.48(1H,dd); 3.74(1H) ppm. ^{1}H NMR of other component 0.88(3H,d), 1.08-2.35(5H, complex), 2.97(1H,t); 3.64(1H) ppm.

EXAMPLE 2

Stage 1

To a cooled solution of tetrahydrophthalic anhydride (50g) in dry N,N-dimethylformamide (250 ml) at 5°C was added sodium methoxide (18g) at such a rate that the temperature did not exceed 10°C. The reaction mixture

was stirred at room temperature for 1½ hours, cooled to 5°C and then benzyl bromide (39ml) was added. After allowing it to stand at room temperature for 2 days, the reaction mixture was poured into water and extracted with diethyl ether (ether). The combined ether extracts were washed with aqueous sodium bicarbonate solution, dried over anhydrous sodium sulphate and evaporated in vacuo to leave methyl benzyl cis-cyclohex-4-ene-1,2-dicarboxylate (88g) as a yellow oil.

Stage 2

Methyl benzyl cis-cyclohex-4-ene-1,2-dicarboxylate (88g) was added in portions to a rapidly stirred solution of potassium permanganate (161g) in water (600ml) keeping the temperature in the range of 15-25°C by use of an ice-bath. The reaction mixture was stirred for 6 hours at room temperature and allowed to stand overnight. The reaction mixture was then treated with sulphur dioxide (keeping the temperature below 20°C) until all manganese dioxide present had been reduced. The mixture was then filtered and the filtrate and residue extracted with ethyl acetate. The ethyl acetate extracts were combined, dried over anhydrous sodium sulphate and evaporated to dryness to leave a gummy white solid. This was triturated with hexane/diethyl ether to give cis-3-benzyloxycarbonyl-4-methoxycarbonyl-hexan-1,6-dioic acid (51g) as a white powder.

Stage 3

A mixture of cis-3-benzyloxycarbonyl-4-methoxycarbonylhexan-1,6-dioic acid (85g), anhydrous sodium acetate (17.3g) and acetic anhydride (300ml) was heated at 130°C for 5 hours. After cooling the mixture was filtered and the filtrate distilled to remove acetic anhydride. The oil which remained was chromatographed on silica eluting with n-hexane: ethyl acetate 2:1 to give an amber oil. The amber oil was dissolved in diethyl ether and the solution was cooled to -70°C. After scratching, methyl benzyl cis-4-oxocyclopentane-1,2-dicarboxylate (67g) crystallised.

Stage 4

Methyl benzyl cis-4-oxocyclopentane-1,2-dicarboxylate (17g) was dissolved in methanol (120ml), 5% palladium on charcoal (catalyst) added, and hydrogenolysed at 3 bar for two hours. The catalyst was filtered off and the filtrate evaporated to leave methyl hydrogen cis-4-oxocyclopentane-1,2-dicarboxylate (8.8g) as a brown oil which crystallised on

standing.

Stage 5

To solution of methyl hydrogen cis-4-oxocyclopentane-1,2-dicarboxylate (5.3g) in dry dichloromethane (50ml) was added oxalyl chloride (3.3ml) over 20 minutes. Drops of N,N-dimethylformamide (catalyst) were added occasionally over the 20 minute period. After the addition was complete reaction mixture was stirred for one hour. Tetra-n-butylammonium bromide (catalytic amount) was then added followed by a solution of sodium azide (3.1g, in the minimum amount of water necessary for solution). The resulting reaction mixture was stirred for an hour, and the organic phase was separated, dried over anhydrous magnesium sulphate and filtered. The filtrate was filtered thourgh a 2cm plug of silica. The resulting filtrate was partially concentrated, benzyl alcohol (20ml) added and the remainder of the dichloromethane distilled off. The reaction mixture was heated at 100°C for 3 hours and the solvent removed by distillation at 0.1mm Hg, 110°C to leave an oil. Methyl cis-2-(benzyloxycarbonyl)amino-4-oxocyclopentane-1-carboxylate (3.4g, Compound No. 11 in Table I) was crystallised from the oil using a mixture of ethyl acetate and n-hexane as solvent.

Stage 6

To a mixture of methyl cis-2-(benzyloxycarbonyl)amino-4--oxocyclopentane-1-carboxylate (1.15g) in methanol (10ml) was added, in three portions, sodium borohydride (75mg). The reaction mixture was stirred for 30 minutes, poured into 5% aqueous hydrochloric acid and the resulting mixture was extracted with ethyl acetate. The combined extracts were dried over anhydrous mangesium sulphate and evaporated to leave methyl 1,2-cis-2-(benzyloxycarbonyl)amino-4-hydroxycyclopentane-1-carboxylate as a mixture of epimers at C4 (a 9:1 mixture of 2,4-trans:2,4-cis; Compound No. 12 of Table I).

Stage 7

To a cooled and stirred solution of the product of Stage 6 (1.25g) in 1,2-dichloroethane (25ml) was added diethylaminosulphur trifluoride (690µl). After 15 minutes, the reaction mixture was quenched with ethanol, added to saturated aqueous sodium bicarbonate solution and the aqueous extracted with dichloromethane. The combined extracts were washed with water, dried over anhydrous magnesium sulphate and evaporated. The residue was purified by chromatography on silica (eluant n-hexane:ethyl acetate

2:1) to give a colourless solid. The solid was recrystallised from a mixture of n-hexane and ethyl acetate to yield methyl 1,2-cis-2-(benzyloxycarbonyl)amino-4-fluorocyclopentane-1-carboxylate as a mixture of epimers at C4 (Compound No. 4 of Table I; a 9:1 mixture of 2,4-cis:2,4-trans) as colourless needles (m.pt. 80-82.5°C).

Stage 8

A mixture of the product of Stage 7 (590mg), methanol (10ml), concentrated hydrochloric acid (1ml) and 5% palladuim on charcoal (catalyst) were hydrogenolysed at 3 bar for 2 hours and then at 6 bar for one hour. The catalyst was filtered off and the filtrate evaporated to leave methyl 1,2-cis-2-amino-4-fluorocyclopentane-1-carboxylate hydrochloride as a mixture of epimers at C4 (a 9:1 mixture of 2,4-cis:2,4-trans).

Stage 9

A mixture of all of the product of Stage 8 was heated for one hour at 80°C in aqueous hydrochloric acid. The reaction mixture was then evaporated to dryness to leave a powder. The powder was washed with acetone and diethyl ether and dried to leave 1,2-cis-2-amino-4-fluoro-cyclopentane-1-carboxylic acid hydrochloride as a mixture of epimers at C4 (Compound No. 2 of Table I; a 9:1 mixture of 2,4-cis:2,4-trans).

EXAMPLE 3

Stage 1

To a solution of methyl hydrogen cis-4-oxocyclopentane-1,2--dicarboxylate (526mg), prepared as in Stage 4 of Example 2, in dry dichloromethane (5ml) was added, portionwise, oxalyl chloride (330µl). A drop of N,N-dimethylformamide was added as catalyst and the reaction mixture was stirred for 1.5 hours. The resulting solution was added to a vigorously stirred solution of sodium azide (245mg) and tetra-n-butyl-ammonium bromide (catalytic amount) in water (5ml). After the reaction mixture had been stirred for an hour, the organic phase was separated and dried over anhydrous sodium sulphate. After filtration the filtrate (which was a solution of Compound No. 8 of Table I) was added to refluxing tert-butanol (15ml) over 1 hour. The reaction mixture was then refluxed for a day after which the solvent was removed by distillation. The residue was taken-up in ethyl acetate and the organic solution, washed with saturated aqueous sodium bicarbonate solution, dried, evaporated and the

residue chromatographed on silica eluting with n-hexane:ethyl acetate 1:1. After evaporation of solvents, methyl cis-2-(tert-butoxycarbonyl)amino-4--oxocyclopentane-1-carboxylate (Compound No. 7 of Table I) was provided as a solid (m.pt. 132-133.5°C).

Stage 2

To a mixture of the product of Stage 1 (220mg) in dry dichloromethane (3ml) was added diethylaminosulphur trifluoride (170µl, and a further 170µl after several hours). The reaction mixture was poured onto saturated aqueous sodium bicarbonate solution and stirred until there was no further effervescence. This mixture was extracted with dichloromethane, the extracts were combined, dried over anhydrous sodium sulphate and evaporated. The residue was chromatographed on silica using diethyl ether:n-hexane 1:1 as eluant to provide methyl cis-2-(tert-butoxy-carbonyl)amino-4,4-difluorocyclopentane-1-carboxylate (Compound No. 9 of Table I; 135mg) as a pale yellow solid (m.pt. 82-83.5°C).

Stage 3

To a solution of the product of Stage 2 (510mg) in tetrahydrofuran (4ml) were added lithium hydroxide (77mg) and water (1ml). The resulting mixture was refluxed for one hour, diluted with water and washed with ethyl acetate. The aqueous was then acidified with an aqueous solution of citric acid and extracted with ethyl acetate. The extracts were combined, dried with anhydrous sodium sulphate and evaporated to leave a solid. The solid was recrystallised to leave cis-2-(tert-butoxycarbonyl)amino-4,4--difluorocyclopentane-1-carboxylic acid (Compound No. 10 of Table I).

Stage 4

A mixture of the product of Stage 3 (300mg), trifluoroacetic acid (1ml) and dichloromethane (1ml) was allowed to stand for 20 minutes after which time it was evaporated to dryness and the residue dissolved in 2N aqueous hydrochloric acid. The solution was evaporated to dryness and the residue washed with acetone and dried under vacuum to leave cis-2-amino--4,4-difluorocyclopentane-1-carboxylic acid hydrochloride (165mg, Compound No. 5 of Table I) as a white solid.

EXAMPLE 4

Stage 1

A mixture of methyl cis-2-(benzyloxycarbonyl)amino-4-oxocyclopentane--1-carboxylate (335mg, prepared as described in Stage 5 of Example 2),

concentrated hydrochloric acid (0.5ml) and 5% palladium on charcoal (catalytic amount) in methanol (5ml) was hydrogenolysed at 1 bar for 15 minutes. The reaction mixture was filtered and the filtrate evaporated to dryness to leave a brown gum. The gum was triturated in acetone to give methyl cis-2-amino-4-oxocyclopentane-1-carboxylate hydrochloride (Compound No. 13 of Table I) as a white solid.

Stage 2

A mixture of the product from Stage 1 (85mg) and aqueous hydrochloric acid (1ml) was heated at 80°C for 20 minutes and then evaporated to dryness to cis-2-amino-4-oxocyclopentane-1-carboxylic acid hydrochloride (Compound No. 14 of Table I).

EXAMPLE 5

Stage 1

To a mixture of furan-3,4-dicarboxylic acid (28.65g) in dry dichloromethane (150ml) was added, dropwise and with stirring, oxalyl chloride (40.07ml). After about 5ml of oxalyl chloride has been added DMF (2 drops) was added. After allowing the mixture to stand it was concentrated in vacuo to leave furan-3,4-dicarbonyl chloride as a pale tan solid.

The tan solid was dissolved in dry dichloromethane (100ml) and methanol (50ml) was added dropwise and with cooling and stirring. Further methanol (150ml) was then added followed by triethylamine (63.7ml) which was added dropwise at 0-5°C. The reaction mixture was kept between 0°C and 5°C for 30 minutes and then concentrated in vacuo to leave a solid residue. The residue was triturated with ethyl acetate and water and the water layer was further extracted twice with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous mangnesium sulphate and concentrated in vacuo to leave dimethyl furan-3,4-dicarboxylate as an oil (32.29g) which crystalised on standing m.pt. 45.5-46.5°C).

Stage 2

To a solution of dimethyl furan-3,4-dicarboxylate (5.0g) in methanol (25ml) was added a catalytic amount of rhodium on aluminium oxide. The mixture was hydrogenated at 5 atmospheres for 4 hours. The mixture was filtered and the filtrate concentrated in vacuo to leave dimethyl cis-tetrahydrofuran-3,4-dicarboxylate (5.098g) as a pale yellow oil.

Stage 3

Dimethyl cis-tetrahydrofuran-3,4-dicarboxylate (10.17g) was refluxed in a mixture of concentrated hydrochloric acid (50ml) and water (50ml) for 10 hours. The reaction mixture was cooled and concentrated in vacuo to leave an oil. The oil was taken up in diethyl ether, dried over anhydrous magnesium sulphate and concentrated in vacuo to leave cis-tetrahydrofuran-3,4-dicarboxylic acid (7g) as a yellow gum.

The yellow gum was refluxed in acetic anhydride (100ml) for 4.5 hours then cooled and concentrated in vacuo to leave an oil that was cooled and triturated with a mixture of diethyl ether and dichloromethane. Filtration gave tetrahydrofuran-3,4-dicarboxylic anhydride as a greyish solid. The filtrate was evaporated and the residue distilled at 10-15mm Hg in the range 180-250°C to yield a further amount of the anhydride as an oil which crystallised on standing. (Total yield: 6.575g).

Stage 4

To a cooled suspension of pentane-washed sodium hydride (0.845g of a 60% dispersion in mineral oil) in dry DMF was added, dropwise, a solution of benzyl alcohol (2.28g) in dry DMF. The resulting mixture was stirred at 0°C for 0.5 hour and at 20°C for 1 hour. The mixture was then cooled to 5°C and a solution of tetrahydrofuran-3,4-dicarboxylic anhydride in dry DMF (15ml) was added dropwise. The mixture was stirred for 2.5 hours at room temperature and allowed to stand overnight. The reaction mixture was poured into ice water, acidified to pH2 with concentrated hydrochloric acid and then the aqueous mixture was extracted with diethyl ether. The organic extracts were combined, washed with water and then with brine then dried with anhydrous mangnesium sulphate and evaporated in vacuo to leave an oil. The oil was taken up in dichloromethane, and the solution was washed with saturated aqueous sodium bicarbonate solution (twice). The aqueous washings were combined, brought to pH2 with concentrated hydrochloric acid and repeatedly extracted with dichloromethane. The extracts were combined, washed with water and then with brine, dried over anhydrous mangesium sulphate and concentrated in vacuo to leave benzyl hydrogen cis-tetrahydrofuran-3,4-dicarboxylate.

Stage 5

To a stirred solution of benzyl hydrogen cis-tetrahydrofuran-3,4--dicarboxylate (1.0g) in dry dichloromethane (10ml) at 15°C was added

oxalyl chloride (0.45ml). The reaction mixture was stirred at 20°C for 30 minutes and then a drop of DMF was added. The mixture was stirred for 30 minutes at 20°C and for 2 hours at 40°C after which time it was cooled and concentrated in vacuo to leave benzyl cis-3-chloroformyltetrahydrofuran-4-carboxylate as a pale oil.

The pale oil was dissolved in dry toluene (20ml) at 20°C and trimethylsilylazide (1.59ml) was added. The reaction mixture was gradually brought to reflux. After 1½ hours, the mixture was cooled, concentrated in vacuo, and taken up in toluene (20ml). Trimethylsilylazide (1.59ml) was added. The mixture was refluxed for 2 hours and further trimethylsilylazide (1.59ml) added. The reaction mixture was refluxed for four hours, cooled and concentrated in vacuo to leave benzyl cis-3-isocyanatotetrahydrofuran-4-carboxylate as a yellow oil.

The yellow oil was dissolved in dry toluene (15ml) and benzyl alcohol (0.62ml) added. The reaction mixture was refluxed for 1.5 hours and concentrated in vacuo to leave an oil. The oil was taken up in dichloromethane and the organic phase was washed with water and with brine, dried over anhydrous magnesium sulphate and concentrated in vacuo to leave an oil which was distilled at 15mm Hg at 200°C to remove excess benzyl alcohol. The oil remaining was chromatographed on silica eluting first with dichloromethane to remove byproducts and then with diethyl ether to give benzyl cis-3-(benzyloxycarbonyl)aminotetrahydrofuran-4-carboxylate (Compound No. 3 of Table II) as an oil (0.717g).

EXAMPLE 6

Stage 1

A mixture of benzylamine (80ml) and chloromethyltrimethylsilane (35ml) was refluxed for 5 hours and then allowed to stand at room temperature for 2 days. The precipitate which had formed was filtered off and washed with toluene. The filtrate and washings were combined, washed with 15% aqueous potassium hydroxide solution, dried over anhydrous magnesium sulphate and the solvent removed in vacuo to leave an oil. The oil was purified by chromatography on silica eluting with a mixture of ethyl acetate and n-hexane to give N-(trimethylsilylmethyl)benzylamine (35.05g).

Stage 2

N-(Trimethylsilylmethyl)benzylamine (11.75g) was added slowly to an ice cooled solution of formaldehyde (6ml of a 37% solution in water) and

methanol (3ml). The resulting mixture was allowed to warm to room temperature, stirred for 4 hours and solid potassium carbonate added. The mixture was extracted with diethyl ether, the ether extracts were combined, dried over potassium carbonate and the solvent was removed in vacuo to leave an oil. The oil was distilled to give N-trimethylsilyl-methyl-N-(methoxymethyl)benzylamine (8.6g) boiling at 62-68°C at 0.1mm Hg.

This product was mixed with maleic anhydride (3.6g) in tetrahydrofuran (80ml) and the resulting mixture was stirred at room temperature. Caesium fluoride (1.1g) was added, after which the mixture was cooled with an ice salt bath before trimethylsilyltriflate (1.3ml) was added dropwise. The mixture was stirred for 2.5 hours and allowed to stand. Saturated aqueous sodium bicarbonate solution (40ml) was added to the ice cooled reaction mixture. The mixture was extracted with diethyl ether. The extracts were combined, dried with anhydrous magnesium sulphate, filtered and the solvent removed from the filtrate in vacuo to leave cis-1-benzylpyrrolidine-3,4--dicarboxylic acid as an orange paste (7.6g).

Stage 3

A mixture of the product of Stage 2 (7.6g) and acetic anhydride (50ml) was refluxed for 1.5 hours. The solvent was removed in vacuo to leave an oil. The oil was taken up in methanol (60ml), the resulting solution was cooled in an ice bath, and sodium methoxide (1.56g) was added portionwise. The resulting mixture was stirred for 2 hours at room temperature, allowed to stand overnight and then poured into a pH6 buffer. This mixture was extracted with dichloromethane, taken to pH6 again and extracted with dichloromethane. The aqueous layer was then reduced in volume in vacuo to leave an off-white solid which was purified by ion-exchange column chromatography (Dowex acid resin) eluting first with water and then with 0.3M aqueous ammonia solution to provide methyl hydrogen cis-1-benzyl-pyrrolidine-3,4-dicarboxylate (4.2g).

Stage 4

To a stirred suspension of the product of Stage 3 (2.0g) in dichloromethane (30ml) was added slowly oxalyl chloride (0.84ml). After 20 minutes a few drops of DMF were added to the reaction mixture. A solution of sodium azide (0.64g) and tetra-n-butylammonium bromide (catalytic amount) in water (2ml) was then added and the resulting mixture stirred for 2.5 hours. The organic phase was then separated, dried over anhydrous

magnesium sulphate and some of the solvent was removed. tert-Butanol (50ml) was then added to the solution and the resulting mixture was refluxed for 3 hours after which time the solvent was removed in vacuo. The residue was dissolved in dichloromethane, the organic solution was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulphate and the solvent was removed in vacuo to leave an oil which was chromatographed on silica eluting with 45% ethyl acetate in n-hexane to provide methyl cis-1-benzyl-3-(tert-butoxycarbonyl)amino-pyrrolidne-4-carboxylate (Compound No. 8 of Table II) as a colourless oil.

Stage 5

A mixture of the product of Stage 4 (0.3g) and concentrated hydrochloric acid (3ml) were stirred together at room temperature for 1 hour and then at 80°C for 2 hours. The water was removed in vacuo to leave cis-1-benzyl-3-aminopyrrolidine-4-carboxylic acid hydrochloride (0.2g; Compound No. 10 of Table II) as a foam.

EXAMPLE 7

The compounds were tested against the diseases Plasmopora viticola on vine and Phytophthora infestans lycopersici on tomato. The technique employed was as follows.

The plants were grown in John Innes Potting Compost (No. 1 or 2) in 4cm diameter minipots. The test compounds were formulated either by bead milling with aqueous DISPERSOL T or as a solution in acetone or acetone/ethanol which was diluted to the required concentration immediately before use. The formulations (100 ppm active ingredient) were sprayed onto the foliage of the plants or to the roots of the plants in the soil. The sprays were applied to maximum retention and the root drenches to a final concentration equivalent to approximately 40 ppm in dry soil.

For most of the tests the compounds were applied to the soil (roots) or to the foliage (by spraying) one or two days before the plant was inoculated with the disease. When applying the pathogens to the leaves of test plants, the pathogens were applied by spray as a spore suspension. After inoculation, the plants were put into an appropriate environment to allow infection to proceed and then incubated until the disease was ready for assessment. The period between inoculation and assessment varied from four to seven days according to the disease and environment.

The disease control was assessed by visual assessment of the percentage leaf area covered by actively sporulating disease. Assessments were performed on a single leaf of each of the two replicate plants, and the mean value of these two recordings was calculated for each treatment. The mean value for each treatment was then expressed as a percentage of the level of disease present on the untreated control plants. This calculated value is referred to as a POCO (Percentage of Control) value. An example of a typical calculation is as follows:

Mean disease level on untreated Control = 90

Mean disease level on treatment A = 30

$$\text{POCO for treatment A} = \frac{\text{Mean disease level on treatment A}}{\text{Mean disease level on untreated Control}} \times 100$$

$$= \frac{30}{90} \times 100 = 33.3$$

Thus a POCO value of 0 indicates complete disease control.

The results are shown in Table IV.

TABLE IV

COMPOUND (Table No.)	Pv prot	Pv syst	Pil prot	Pil syst
2(I)	71*	0	84"	55
3(I)	82*	32	50"	98
4(I)	77*	109	62"	100
5(I)	103*	57	104"	76
15(I)	89*	0	-	-
16(I)	90$	0$	115"	90$
17(I)	90$	30$	112"	90$

TABLE IV (Continued)

COMPOUND (Table No.)	Pv prot	Pv syst	Pil prot	Pil syst
20(I)	82*	33	100"	100
34/36(I)£	53*	0	100"	0
32(I)	0*	0	0"	1
40(I)	0*	0	43"	0
1(II)	108*	36	100"	100
3(II)	108*	61	100"	100
10(II)	68*	68	100"	101
11(II)	47*	94	111"	100

Pv	=	Plasmopara viticola
Pil	=	Phytophthora infestans lycopersici
prot	=	foliar spray
syst	=	root drench

* = tested at 50ppm

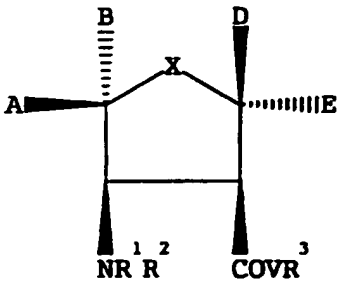
" = tested at 200ppm

$ = tested at 25ppm

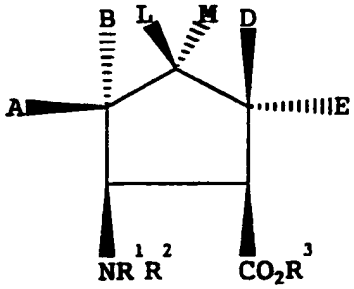
£ = a 7:1 mixture of compounds 34:36 of TABLE I

CHEMICAL FORMULAE

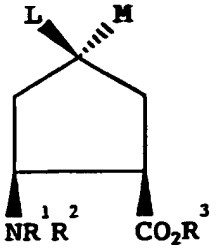
(IN DESCRIPTION)



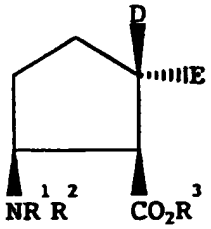
(I)



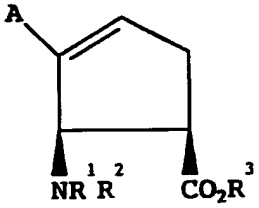
(I.1)



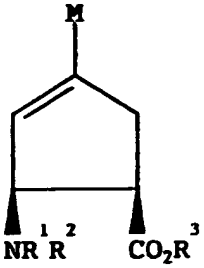
(I.1b)



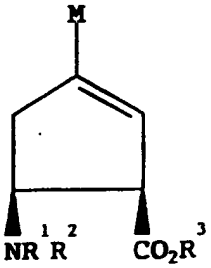
(I.1c)



(I.1d)



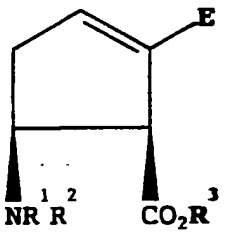
(I.1e)



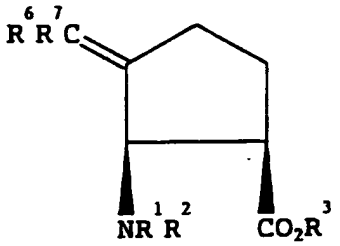
(I.1f)

CHEMICAL FORMULAE

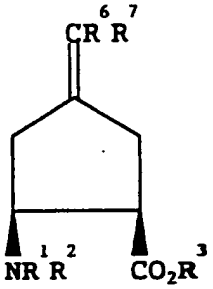
(IN DESCRIPTION)



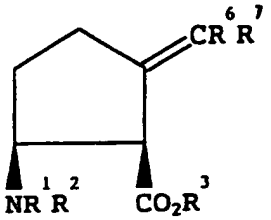
(I.1g)



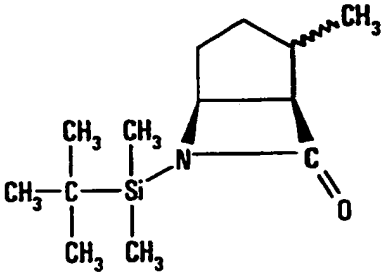
(I.1h)



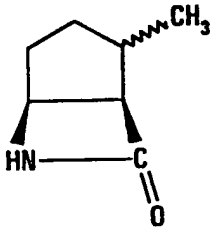
(I.1i)



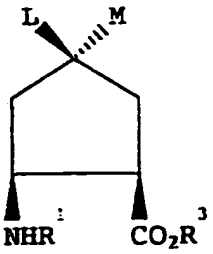
(I.1j)



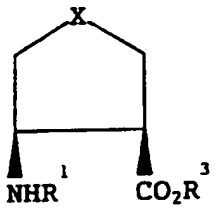
(VI)



(V)

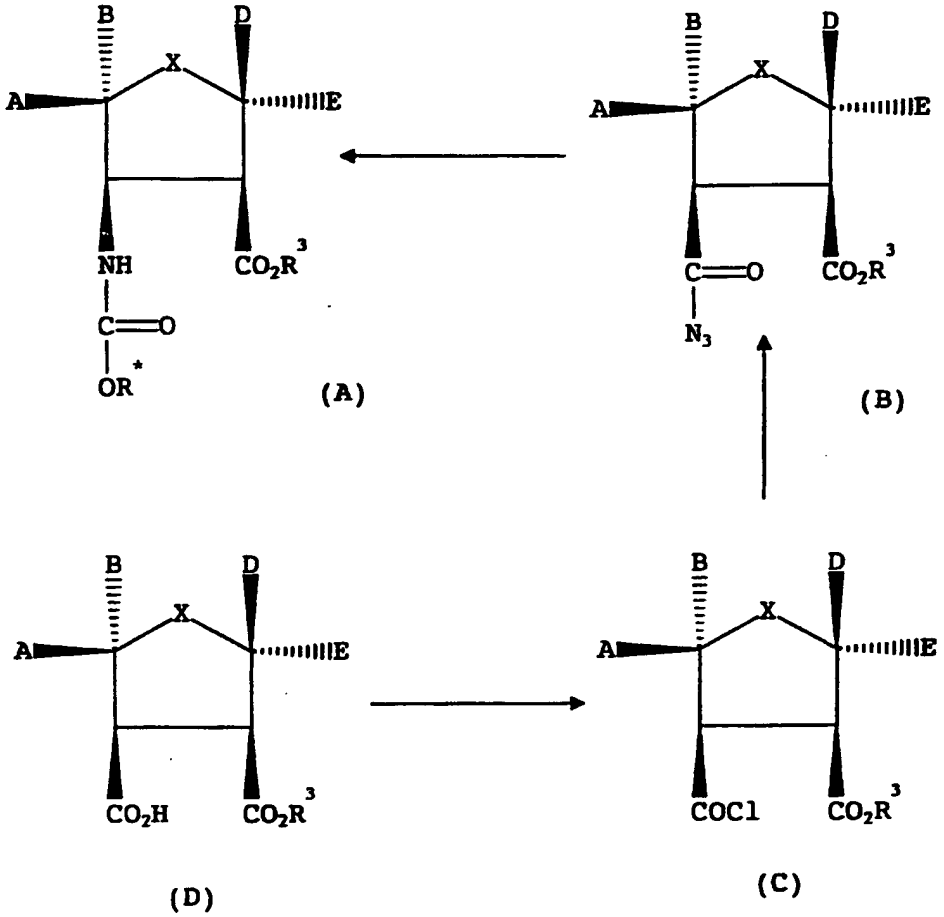


(I.2)



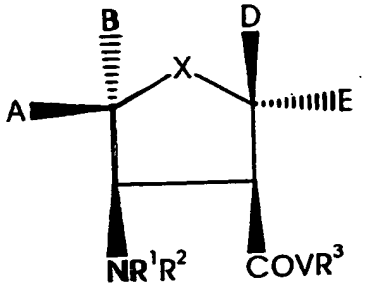
(I.3)

SCHEME 1


B
D
X
A
E
NH
CO_2R^3
C=O
OR*
(A)
B
D
X
A
E
C=O
CO_2R^3
N_3
(B)
B
D
X
A
E
CO_2H
CO_2R^3
(D)
B
D
X
A
E
COCl
CO_2R^3
(C)

CLAIMS

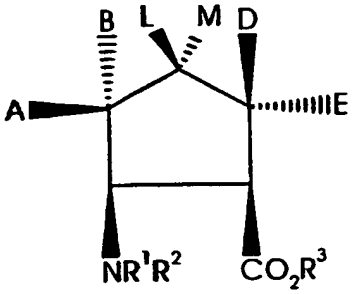
1. A method of combating fungi which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I):



(I)

wherein X is O, S, SO, SO_2, NR^8 or CLM; A, B, D, E, L and M are, independently, hydrogen, halogen, alkyl, mono- or di-haloalkyl, benzyl (optionally substituted by halogen or haloalkyl) or hydroxy; A and B or D and E or L and M may together form a =S, =O or $=CR^6R^7$ group; B and L or D and L may together form a bond; V is O or NR^4; R^1 and R^2 are, independently, hydrogen or an amine protecting group; R^3, R^4 and R^8 are, independently, hydrogen, alkyl or benzyl; R^6 and R^7 are, independently, hydrogen, halogen, alkyl, phenyl, benzyl, alkoxy or acyloxy; or a salt thereof; provided that when X is CLM, R^1, R^2, R^3, A, M, D and E are all hydrogen, L and B are either both hydrogen or together form a bond, and V is O then the compound of formula (I) is in the form of a salt, but not a hydrochloride salt.

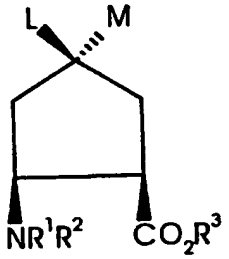
2. A method as claimed in claim 1 which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1):



(I.1)

wherein A, B, D, E, L and M are, independently, hydrogen, halogen, alkyl, mono- or di-haloalkyl or hydroxy; or A and B or D and E or L and M many together form a $=CR^6R^7$ group; or B and L or D and L may together form a bond; R^6 and R^7 are, independently, hydrogen, halogen, alkyl, phenyl, benzyl, alkoxy or acyloxy; R^1 is hydrogen and R^2 is hydrogen or an amine protecting group; and R^3 is hydrogen, alkyl or benzyl; or a salt thereof.

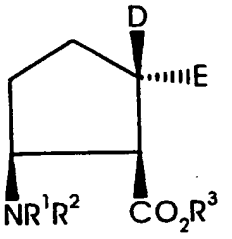
3. A method as claimed in claim 2 which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1b):



(I.1b)

wherein L and M are independently hydrogen, halogen, alkyl, mono- or di-haloalkyl or hydroxy; and R^1, R^2 and R^3 are as defined in claim 2; or a salt thereof.

4. A method as claimed in claim 2 which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1c):

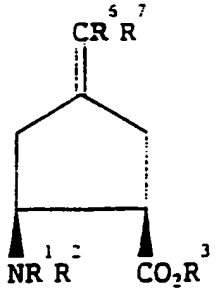


(I.1c)

wherein D and E are independently hydrogen, halogen, alkyl, mono- or di-haloalkyl or hydroxy; and R^1, R^2 and R^3 are as defined in claim 2; or a salt thereof.

5. A method as claimed in claim 4 wherein D is hydrogen, E is alkyl, and R^1, R^2 and R^3 are as defined in claim 2; or a salt thereof.

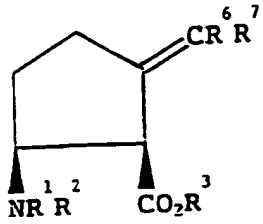
6. A method as claimed in claim 2 which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1i):



(I.1i)

wherein R^6 and R^7 are, independently, hydrogen, halogen, alkyl, phenyl, benzyl, alkoxy or acyloxy; and R^1, R^2 and R^3 are as defined in claim 2; or a salt thereof.

7. A method as claimed in claim 2 which comprises applying to a plant, to a seed of a plant or to the locus of a seed or plant a compound of formula (I.1j):

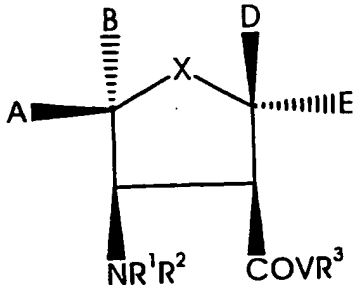


(I.1j)

wherein R^6 and R^7 are, independently, hydrogen, halogen, alkyl, phenyl, benzyl, alkoxy or acyloxy; and R^1, R^2 and R^3 are as defined in claim 2; or a salt thereof.

8. A method as claimed in any one of the preceeding claims wherein R^1, R^2 and R^3 are all hydrogen.

9. A compound of formula (I):



(I)

wherein:

(a) when X is CLM, A, B, D, E and R^2 are hydrogen and V is oxygen then:

i) L and R^3 are H, M is F and R^3 is H or tert-butoxycarbonyl; or

ii) L and M are F, R^3 is tert-butoxycarbonyl and R^1 is H or CH_3; or

iii) L and M together with the carbon to which they are attached form C=O, R^1 is methyl and R^3 is H, tert-butoxycarbonyl, $C(O)CH_3$ or $C(O)NHC(O)OC(CH_3)_3$; or

iv) L is OH, M is H, R^1 is CH_3 and R^3 is tert-butoxycarbonyl; or a salt thereof; or

(b) when A, B, D, E and R^2 are hydrogen and V is oxygen then R^1 is tert-butoxycarbonyl, R^3 is CH_3 and X is SO_2, SO, NH or $NCH_2C_6H_5$; or R^1 and R^3 are both H and X is NH; or R^1 is tert-butoxycarbonyl, R^3 is $CH_2C_6H_5$ and X is oxygen; or a salt thereof; or

(c) when X is CLM and R^1, R^2, R^3, A and M are all hydrogen then:

i) B is fluorine and L, D and E are all hydrogen;

ii) L is fluorine and B, D and E are all hydrogen;

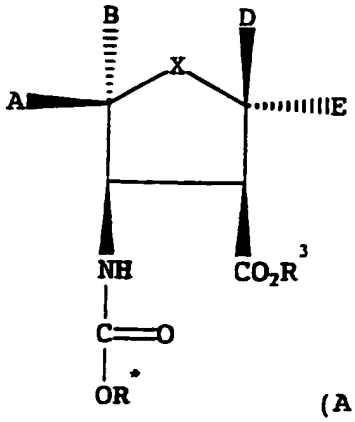
iii) D is fluorine, ethyl, tert-butyl or benzyl and B, L and E are all hydrogen;

iv) E is fluorine and B, L and E are all hydrogen; or

v) D and E together form $=CH_2$ and B and L are both hydrogen; or a salt thereof.

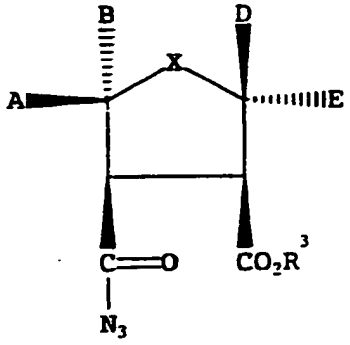
10. A fungicidal composition comprising a compound as claimed in claim 9 and a fungicidally acceptable carrier or diluent.

11. A process for preparing a compound of formula (A):



(A)

wherein A, B, D, E and X and R^3 are as defined in claim 1, but R^3 is not hydrogen, and R^* is alkyl, phenyl or phenylalkyl (the phenyl rings being optionally substituted by alkyl, halogen, haloalkyl, alkoxy or nitro), the process comprising reacting a compound of formula (B):



(B)

wherein A, B, D, E, X and R^3 are as defined above, with an alcohol of formula R^*OH in the presence of a solvent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 94/01751

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A01N37/44 A01N37/46 A01N43/08 A01N43/10 A01N43/36
A01N47/18 C07C229/48 C07C271/24 C07D207/16 C07D307/24
C07D333/38 C07D333/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A01N C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL PATENTS INDEX, BASIC ABSTRACTS JOURNAL Week 8821, Derwent Publications Ltd., London, GB; AN 88-142651/21 & JP,A,63 083 004 (IHARA) 13 April 1988 see abstract ---	1-4,8
X	CHEMICAL PATENTS INDEX, DOCUMENTATION ABSTRACTS JOURNAL Week 8902, Derwent Publications Ltd., London, GB; AN 89-011885/02 & JP,A,63 287 753 (IHARA) 24 November 1988 see abstract --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
11 October 1994	25. 10. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Decorte, D

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 94/01751

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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